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Comparative Analysis of the Electrostatic Potentials of Dibenzofuran and Some Dibenzo-*p*-dioxins

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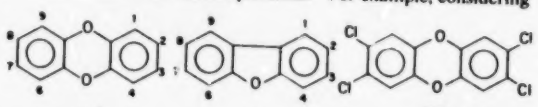
Abstract: Electrostatic potential maps of dibenzofuran, dibenzo-*p*-dioxin, 2,8-dichloro-3,7-dimethyldibenzo-*p*-dioxin, 2,3,7,8-tetrafluorodibenzo-*p*-dioxin, and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) are presented and compared. The biological activities of these molecules increase from zero for the first two to very strong for the highly toxic TCDD. The analysis of the electrostatic potentials suggests certain key features that may be necessary for the effective interaction of these classes of compounds with a cytosolic receptor, which is believed to be the initial step leading to various toxic responses and other biological activity.

Dibenzo-*p*-dioxin (I) and dibenzofuran (II) are the parent compounds for large families of derivatives, having halogens and other substituents at various positions. For example, considering



I II III

just chlorine as a substituent, there are 75 possible derivatives of I (containing 1–8 chlorines) and 135 such derivatives of II. When bromine, fluorine, and other types of substitution are taken into account, there are clearly hundreds of possible compounds. These have varying degrees of toxicity, ranging from zero to very high; the latter is exemplified by the notorious 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD, III). The toxic responses elicited by these compounds include gastric lesions, hepatotoxicity, carcinogenesis, loss of lymphoid tissue, acute loss of weight, and chloracne.[1,2]

To differing extents, the substituted dibenzo-*p*-dioxins and dibenzofurans also induce aryl hydrocarbon hydroxylase (AHH) activity.[3] This is a microsomal monooxygenase system that is involved in the metabolic conversion of carcinogenic aromatic hydrocarbons to their active forms.[4]

Studies of a series of halogenated dibenzo-*p*-dioxins and dibenzofurans have revealed a good correlation between potency

(1) Windholz, M., E. "The Merck Index", 10th ed.; Merck and Co.: Rahway, NJ, 1983; p 8957.
(2) Poland, A.; Knutson, J. C. *Annu. Rev. Pharmacol. Toxicol.* **1982**, *22*, 517–554.
(3) Poland, A.; Glover, E. *Mol. Pharmacol.* **1973**, *9*, 736–747.
(4) (a) Harvey, R. G. *Acc. Chem. Res.* **1981**, *14*, 218–226. (b) Guengerich, F. P.; Macdonald, T. L. *Acc. Chem. Res.* **1984**, *17*, 9–16.

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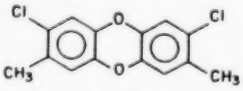
for inducing AHH activity and toxicity.[3] It was also found that certain structural requirements for both types of activity could be identified:[3] (a) At least three of the four lateral positions (2,3,7, and 8) must have halogen substituents (especially chlorine or bromine). The activity is greater if all four of these positions are halogenated. (b) The activity induced by halogen substituents decreases in the order Br > Cl > F. (c) At least one ring position must remain unsubstituted.

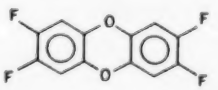
The available evidence indicates that the toxic effects produced by dibenzo-*p*-dioxins and dibenzofurans are related to their interactions with a cytosolic receptor.[2,5] This receptor is believed to be a protein and has been characterized by Carlstedt-Duke et al. by gel filtration and ultracentrifugal sedimentation. The same receptor is apparently involved in the AHH induction, since a study of 23 halogenated dibenzo-*p*-dioxins and dibenzofurans produced an excellent correlation between binding affinity for the cytosolic receptor and effectiveness in inducing AHH activity.[2]

The interaction of a molecule with a receptor is an example of a "recognition" process, in which the receptor recognizes that the molecule has certain key features that will promote their interaction. This precedes the formation of any covalent bonds. In the past, such key features have been successfully identified through the analysis of the electrostatic potential that the molecule's nuclei and electrons create in the surrounding space. It is through this potential that the molecule initially interacts with any other system in its vicinity. In a number of cases, the affinity of a particular molecule for a specific receptor has been shown to depend upon the degree to which the electrostatic potential of the former possesses certain characteristics that have been established as being required for effectively interacting with that receptor.[7]

A knowledge of this essential electrostatic potential pattern (which is likely to involve certain relative orientations and magnitudes of positive and negative potentials) leads to important insights into the nature of the interaction and of the receptor itself. It also provides a predictive capability, since once the elements of the potential that are associated with toxicity have been determined, molecules of unknown activity can be evaluated by ascertaining to what extent their potentials possess these characteristics. As an initial step in achieving these objectives for the substituted dibenzo-*p*-dioxins and dibenzofurans, we have calculated the electrostatic potentials of dibenzo-*p*-dioxin (I), dibenzofuran (II), 2,8-dichloro-3,7-dimethyldibenzo-*p*-dioxin (IV), 2,3,7,8-tetrafluorodibenzo-*p*-dioxin (*V*), and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD, III).



IV



V

Methods

The electrostatic potential $V(\mathbf{r})$ that is produced at any point r by the nuclei and electrons of a molecule is expressed rigorously by:

$$V(\mathbf{r}) = \sum_A \frac{Z_A}{|\mathbf{R}_A - \mathbf{r}|} - \int \frac{\rho(\mathbf{r}')\, d\mathbf{r}'}{|\mathbf{r}' - \mathbf{r}|} \qquad (1)$$

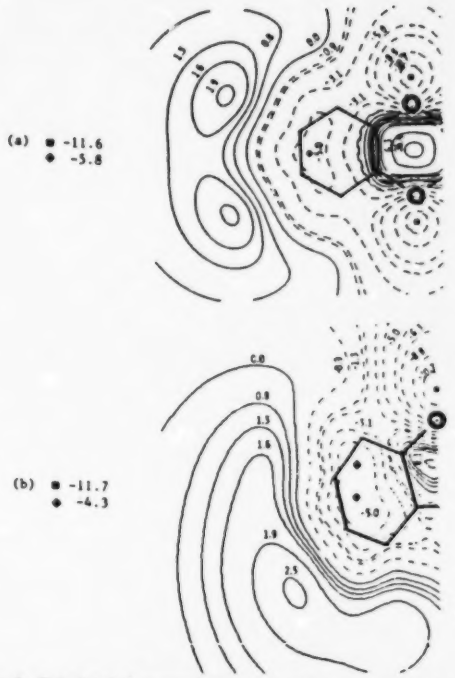


Figure 1. Calculated electrostatic potentials of dibenzo-*p*-dioxin (a) and dibenzofuran (b) in planes 1.75 Å above the molecular plane. Half of each molecule is shown. Positions of most negative potentials are indicated by (■) and (◆), with the corresponding values (in kcal/mol) given at the left.

Z_A is the charge on nucleus A, located at R_A, and $\rho(\mathbf{r})$ is the electronic density function of the molecule, which we obtain by computing an ab initio self-consistent-field molecular wave function. Equation 1 shows that $V(\mathbf{r})$ is the sum of a positive contribution coming from the nuclei and a negative one from the electrons; its sign in any particular region depends, therefore, upon whether the effects of the nuclei or the electrons are dominant in that region.[8] An important feature of the electrostatic potential is the fact that it is a real physical property, one that can be determined experimentally as well as computationally.[9]

We have computed the electrostatic potentials of molecules I–V by using the GAUSSIAN 82 program at the STO-5G level. The geometry of TCDD (III), which is planar, was obtained from crystallographic studies,[10] with the C–H bond lengths taken to be 1.08 Å. Basically the same structure was used for I, IV, and V, with appropriate modifications. For I, all of the chlorines were replaced by hydrogens, at H–C–C angles of 120°. For IV, two chlorines were replaced by methyl groups, their geometries being taken from an optimized toluene structure.[11] One of the methyl hydrogens was positioned in the plane of the aromatic rings, pointing away from the chlorine; the other two were above and

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(6) Carlstedt-Duke, J. M. B.; Harnemu, U. B.; Högberg, B.; Gustafsson, J. A. *Biochim. Biophys. Acta* **1981**, *672*, 131–141.

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(8) For recent reviews of the use of electrostatic potentials in interpreting and predicting molecular reactivity as well as in analyzing drug–receptor and enzyme–substrate interactions, see, for example: (a) Politzer, P.; Daiker, K. C. "The Force Concept in Chemistry"; Deb, B. M., Ed.; Van Nostrand Reinhold: New York, 1981; pp 294–387. (b) Politzer, P.; Laurence, P. R.; Jayasuriya, K. *Env. Health Perspect.* **1985**, *61*, 191–202 (Special Issue on Structure-Activity Correlation in Mechanism Studies and Predictive Toxicology).

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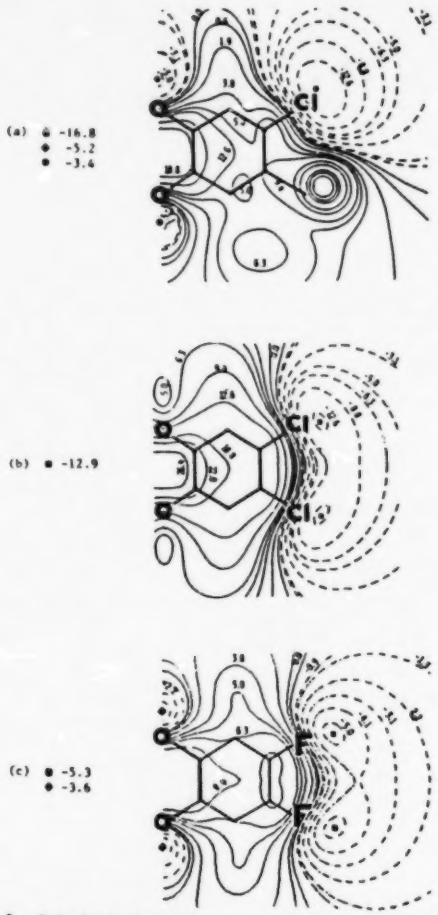

Figure 2. Calculated electrostatic potentials of 2,8-dichloro-3,7-dimethyldibenzo-*p*-dioxin (a), 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (b), and 2,3,7,8-tetrafluorodibenzo-*p*-dioxin (c) in planes 1.75 Å above the molecular plane. The positions of most negative potentials are indicated by (■), (◆), and (●), with the corresponding values (in kcal/mol) given at the left.

below this plane. For V, all chlorines were replaced by fluorines, with C–F bond lengths of 1.35 Å[12] and F–C–C angles of 120°. The dibenzofuran structure was taken from a crystallographic study.[13] The individual rings in this molecule are planar, but overall it has a slight boat form.

Results and Discussion

Our calculated electrostatic potentials for molecules I–V are presented in Figures 1–3.[14] We have focused particularly upon the potential above the plane of each molecule, since this is what the receptor encounters.

For the unsubstituted compounds, I and II, the potential is negative everywhere above the two outer rings (Figure 1). The

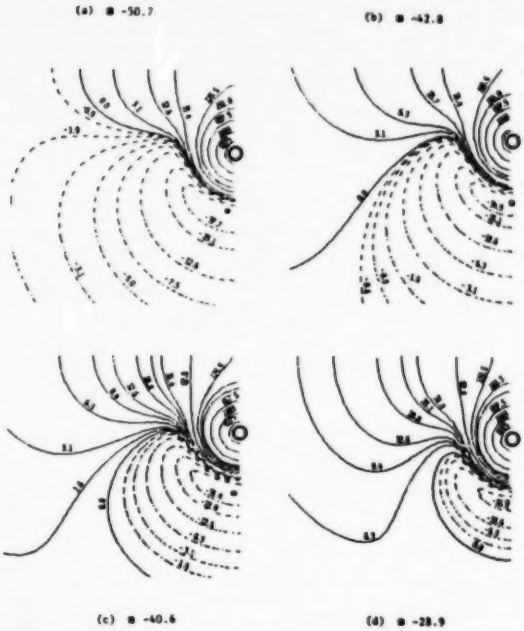

Figure 3. Calculated electrostatic potentials of dibenzo-*p*-dioxin (a), 2,8-dichloro-3,7-dimethyldibenzo-*p*-dioxin (b), 2,3,7,8-tetrafluorodibenzo-*p*-dioxin (c), and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (d) in planes perpendicular to the molecular planes and passing through both oxygens in each molecule. One quarter of the plane is shown for each molecule. Positions of most negative potentials are indicated by (■), with the corresponding values (in kcal/mol) given above and below.

same has been observed in the case of benzene[16] and can be interpreted as being due to the π electrons. There is an even stronger negative region near each oxygen, fully consistent with past experience.[17] Above the central rings, however, the potential is positive. Figure 1 shows a marked similarity between the results for dibenzo-*p*-dioxin and dibenzofuran. Since a crystallographically determined structure was used for the latter, this provides reassurance that the approximate geometry used for dibenzo-*p*-dioxin is a reasonable one.

The introduction of two chlorines, in IV, has a significant effect that reflects the strong electron-attracting inductive power of these substituents; the negative regions above the outer rings are completely eliminated, and those near the oxygens become weaker [Figure 2a]. The strongest negative potentials are now above the two chlorines. With four chlorine substituents in TCDD, even the oxygens no longer have negative potentials at this distance above the molecular plane [Figure 2b]. This is a noteworthy development, since oxygens normally have large and relatively strong negative regions.[17] The chlorines are also less negative in TCDD than in the dichloroderivative, IV, since there are now four of them competing for the polarizable electronic charge in the molecule.

The replacement of chlorines by fluorines in V shows a pattern similar to that of TCDD in the lateral regions of the molecule, though the magnitudes of these negative regions are smaller than those in TCDD by more than 50% [Figure 2c]. Negative potentials near the oxygens are again seen, with magnitudes approximately similar to those in IV. A comparison of Figure 2 parts b and c shows that the chlorines are more effective than the fluorines in withdrawing charge from the remainder of the

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(13) Banerjee, A. *Acta Crystallogr. Sect. B: Struct. Crystallogr. Cryst. Chem.* **1973**, *B29*, 2070–2074.

(14) Electrostatic potentials for some dibenzo-*p*-dioxins have been computed earlier by Cheney[15] and were used to analyze certain aspects of their interactions with the receptor. The wave functions were obtained by the molecular fragment procedure, and a point-charge approximation was used to generate $V(\mathbf{r})$.

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molecule. This is fully consistent with our earlier studies of halogenated epoxides[17] and can be attributed to the greater charge capacity of chlorine.[18]

The most striking change in going from I and II, which are inactive with respect to receptor binding, AHH induction, and toxicity, to the highly active and toxic TCDD is the drastic weakening of the oxygen negative potentials. Figure 3 presents this from another perspective, showing the very extensive and strong negative regions in I shrinking to the small and weak ones that are found in TCDD.

The presence of relatively strong negative potentials along the entire lateral regions of TCDD and their absence or lesser presence in the other four inactive or marginally active molecules suggest that negative lateral regions of a certain minimum strength may play an essential role in the interaction with the receptor. The experimental observation that activity requires at least three halogen substituents on these sites reinforces this view, since the electron-attracting halogens do give rise to negative regions. These are stronger in the case of chlorine than fluorine, which is consistent with the observed greater potency of chlorine in inducing activity. We also speculate that the weakening of the negative region above the oxygens may be a contributing factor to increasing activity.

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